Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma

Dummer, Reinhard ; Hauschild, Axel ; Santinami, Mario ; Atkinson, Victoria ; Mandalà, Mario ; Kirkwood, John M ; Chiarion Sileni, Vanna ; Larkin, James ; Nyakas, Marta ; Dutriaux, Caroline ; Haydon, Andrew ; Robert, Caroline ; Mortier, Laurent ; Schachter, Jacob ; Lesimple, Thierry ; Plummer, Ruth ; Dasgupta, Kohinoor ; Gasal, Eduard ; Tan, Monique ; Long, Georgina V ; Schadendorf, Dirk

Abstract: Background In the previously reported primary analysis of this phase 3 trial, 12 months of adjuvant dabrafenib plus trametinib resulted in significantly longer relapse-free survival than placebo in patients with resected stage III melanoma with BRAF V600E or V600K mutations. To confirm the stability of the relapse-free survival benefit, longer-term data were needed. Methods We randomly assigned 870 patients who had resected stage III melanoma with BRAF V600E or V600K mutations to receive 12 months of oral dabrafenib (at a dose of 150 mg twice daily) plus trametinib (2 mg once daily) or two matched placebos. The primary end point was relapse-free survival. Here, we report 5-year results for relapse-free survival and survival without distant metastasis as the site of the first relapse. Overall survival was not analyzed, since the required number of events to trigger the final overall survival analysis had not been reached. Results The minimum duration of follow-up was 59 months (median patient follow-up, 60 months for dabrafenib plus trametinib and 58 months for placebo). At 5 years, the percentage of patients who were alive without relapse was 52% (95% confidence interval [CI], 48 to 58) with dabrafenib plus trametinib and 36% (95% CI, 32 to 41) with placebo (hazard ratio for relapse or death, 0.51; 95% CI, 0.42 to 0.61). The percentage of patients who were alive without distant metastasis was 65% (95% CI, 61 to 71) with dabrafenib plus trametinib and 54% (95% CI, 49 to 60) with placebo (hazard ratio for distant metastasis or death, 0.55; 95% CI, 0.44 to 0.70). No clinically meaningful between-group difference in the incidence or severity of serious adverse events was reported during the follow-up period. Conclusions In the 5-year follow-up of a phase 3 trial involving patients who had resected stage III melanoma with BRAF V600E or V600K mutations, 12 months of adjuvant therapy with dabrafenib plus trametinib resulted in a longer duration of survival without relapse or distant metastasis than placebo with no apparent long-term toxic effects. (Funded by GlaxoSmithKline and Novartis; COMBI-AD ClinicalTrials.gov number, NCT01682083. opens in new tab; EudraCT number, 2012-001266-15. opens in new tab.)

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ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

In the previously reported primary analysis of this phase 3 trial, 12 months of adjuvant dabrafenib plus trametinib resulted in significantly longer relapse-free survival than placebo in patients with resected stage III melanoma with *BRAF* V600E or V600K mutations. To confirm the stability of the relapse-free survival benefit, longer-term data were needed.

METHODS

We randomly assigned 870 patients who had resected stage III melanoma with *BRAF* V600E or V600K mutations to receive 12 months of oral dabrafenib (at a dose of 150 mg twice daily) plus trametinib (2 mg once daily) or two matched placebos. The primary end point was relapse-free survival. Here, we report 5-year results for relapse-free survival and survival without distant metastasis as the site of the first relapse. Overall survival was not analyzed, since the required number of events to trigger the final overall survival analysis had not been reached.

RESULTS

The minimum duration of follow-up was 59 months (median patient follow-up, 60 months for dabrafenib plus trametinib and 58 months for placebo). At 5 years, the percentage of patients who were alive without relapse was 52% (95% confidence interval [CI], 48 to 58) with dabrafenib plus trametinib and 36% (95% CI, 32 to 41) with placebo (hazard ratio for relapse or death, 0.51; 95% CI, 0.42 to 0.61). The percentage of patients who were alive without distant metastasis was 65% (95% CI, 61 to 71) with dabrafenib plus trametinib and 54% (95% CI, 49 to 60) with placebo (hazard ratio for distant metastasis or death, 0.55; 95% CI, 0.44 to 0.70). No clinically meaningful between-group difference in the incidence or severity of serious adverse events was reported during the follow-up period.

CONCLUSIONS

In the 5-year follow-up of a phase 3 trial involving patients who had resected stage III melanoma with *BRAF* V600E or V600K mutations, 12 months of adjuvant therapy with dabrafenib plus trametinib resulted in a longer duration of survival without relapse or distant metastasis than placebo with no apparent long-term toxic effects. (Funded by GlaxoSmithKline and Novartis; COMBI-AD ClinicalTrials.gov number, NCT01682083; EudraCT number, 2012-001266-15.)

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For patients with high-risk resected melanoma, immune checkpoint inhibitors and BRAF plus MEK inhibitors (dabrafenib plus trametinib) are well-established adjuvant therapies. In such patients, the side-effect profile and long-term benefit of the drugs are important criteria for selecting the appropriate therapy.[1] Immune checkpoint inhibitors that target programmed cell death 1 (PD-1) protein (nivolumab and pembrolizumab) and the targeted therapy combination of dabrafenib plus trametinib have shown significant relapse-free survival benefits and are considered to be current standard-of-care adjuvant therapies. However, the durability of these benefits with continued follow-up remains an important open question.

In extended follow-up from phase 3 trials of the immune checkpoint inhibitor ipilimumab (targeting cytotoxic T-lymphocyte–associated protein 4),[2,3] results in one study showed relapse-free survival in 39% of the patients and overall survival in 60% at 7 years.[2] However, ipilimumab is no longer considered to be a standard-of-care adjuvant therapy after recent advances with anti–PD-1 and BRAF-targeted therapies.[4,5] The primary analyses of phase 3 trials of PD-1 inhibitors in patients who had melanoma with or without a *BRAF* V600 mutation showed significant relapse-free survival benefits at 1 year in comparisons between pembrolizumab and placebo (75.4% vs. 61.0%; hazard ratio, 0.57; 98.4% confidence interval [CI], 0.43 to 0.74; P<0.001) in patients with resected stage III disease[6] and between nivolumab and ipilimumab (70.5% vs. 60.8%; hazard ratio, 0.65; 97.56% CI, 0.51 to 0.83; P<0.001) in patients with resected stage IIIB/IIIC/IV disease.[7] Long-term data regarding relapse-free and overall survival for these agents are not yet available.[6-9]

In the phase 3 COMBI-AD trial involving patients with resected stage III melanoma with *BRAF* V600E or V600K mutations, 12 months of adjuvant dabrafenib plus trametinib resulted in significantly longer 3-year relapse-free survival than placebo (58% vs. 39%; hazard ratio, 0.47; 95% CI, 0.39 to 0.58; P<0.001).[10,11] The 3-year comparison of overall survival between dabrafenib plus trametinib and placebo (86% vs. 77%; hazard ratio, 0.57; 95% CI, 0.42 to 0.79; P=0.0006) in a preplanned interim analysis that was based on a 26% information fraction did not reach the prespecified significance threshold of P=0.000019.[11]

To confirm the long-term stability of the relapse-free survival benefit associated with 12 months of adjuvant dabrafenib plus trametinib, here we report the 5-year analyses, including relapse-free survival and survival without distant metastasis (with distant metastasis as the site of first relapse),[12] based on extended follow-up from the COMBI-AD trial.

Methods

Trial Design, Patients, and Treatment

COMBI-AD is a randomized, double-blind, placebo-controlled, phase 3 trial in which enrollment was conducted from January 2013 through December 2014 at 169 sites in 25 countries. Patients were randomly assigned to receive dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily (combination therapy) or two matched placebos for 12 months. Eligible adults (age, ≥18 years) had undergone complete resection of histologically confirmed stage IIIA melanoma with lymph-node metastasis measuring at least 1 mm, stage IIIB melanoma, or stage IIIC melanoma, according to the criteria of the seventh edition of the American Joint Committee on Cancer cancer-staging manual (AJCC-7). In addition, all the patients had positive results for *BRAF* V600E or V600K mutations, as confirmed in primary tumor or lymph-node tissue by a central reference laboratory. Patients were required to have undergone completion lymphadenectomy (i.e., without clinical or radiographic indication of remaining regional nodal disease) within 12 weeks before randomization and to have an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability). Full inclusion and exclusion criteria have been reported previously.[11]

Patients were stratified according to *BRAF* mutation type (V600E or V600K) and disease stage (IIIA, IIIB, or IIIC). Treatment continued for 12 months or until disease relapse, unacceptable toxic effects, withdrawal of consent, or death, whichever occurred first. Patients were followed up for disease relapse until the first relapse was observed and were then followed for survival. After relapse or trial discontinuation, subsequent anticancer therapy was permitted at the investigator's discretion, and patients were to remain in follow-up for an analysis of sur-

vival. Unblinding was permitted only if knowledge of the trial treatment was essential for appropriate clinical management or if a serious adverse event occurred.

END POINTS

The primary end point was relapse-free survival, which was defined as the time from randomization until disease recurrence or death from any cause. Secondary end points were overall survival, survival without distant metastasis (defined as the time from randomization until the date of the first distant metastasis or death, whichever occurred first),[12] freedom from relapse (defined as the time from randomization until recurrence, with censoring of data for patients who had died from causes other than melanoma or treatment-related toxic effects), and safety. The subgroup analysis of relapse-free survival was performed on the basis of disease stage (per prevailing AJCC-7 criteria at the time of the trial) and was a prespecified analysis to assess the homogeneity of treatment effect; assessment according to the updated AJCC-8 criteria was performed as a post hoc analysis. (A description of these staging criteria is provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.) All the analyses were based on investigator assessment in the intention-to-treat sample (i.e., all the patients who had undergone randomization). According to the trial protocol (available at NEJM.org), patients with a first relapse at a locoregional site were not required to continue follow-up for distant metastases, and their data were censored for the analysis of survival without distant metastasis at the time of locoregional recurrence if follow-up was not complete. Because the protocol-specified number of events had not yet been reached, no overall survival analysis was conducted at the time of the current analysis.

ASSESSMENTS

Imaging with the use of computed tomography, magnetic resonance imaging, or both was initially performed every 3 months; after 24 months, assessments continued every 6 months until 5 years and then every 12 months until relapse or trial completion. Dermatologic assessments to screen for relapse or cutaneous adverse events were performed every 2 months for the 12-month duration of treatment, then every 3 months during the first 24 months of follow-up; subsequent dermatologic evaluations during follow-up continued every 6 months until 5 years and then every 12 months. Adverse events were recorded from administration of the first dose of dabrafenib plus trametinib or placebo until 30 days after discontinuation of the trial treatment. Dose modifications and interruptions were permitted according to the protocol. After the treatment period, reporting of treatment-related adverse events was at investigator discretion. Only treatment-related serious adverse events and new cancers were required to be reported during follow-up.[11]

TRIAL OVERSIGHT

COMBI-AD was initially sponsored by GlaxoSmithKline; dabrafenib and trametinib became assets of Novartis on March 2, 2015, after which Novartis took over sponsorship of the trial. The trial was conducted in accordance with the provisions of the Declaration of Helsinki. The trial protocol was approved by the institutional review board or independent ethics committee at each trial center and has been published previously. All the patients provided written informed consent before enrollment.

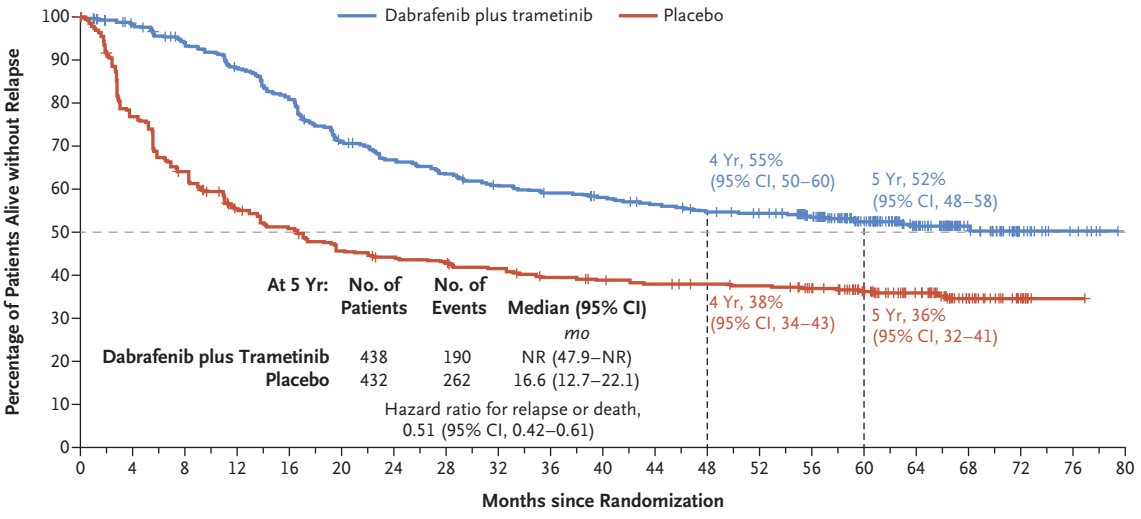
The data were collected by staff members at each trial site and monitored by the sponsor and independent data and safety monitoring committees. The sponsor was also involved in the analysis and interpretation of the data and in the writing of the manuscript. All the authors had full access to all trial data. Editorial support was provided by ArticulateScience and funded by Novartis.

STATISTICAL ANALYSIS

We determined that the enrollment of 870 patients would result in disease relapse or death in approximately 410 patients by the time of the primary analysis (with a two-sided type I error rate of 5%) and would provide a power of more than 90% to detect a hazard ratio of 0.71.

We estimated the duration of survival both without relapse and without distant metastasis using the Kaplan–Meier method and calculated hazard ratios and 95% confidence intervals using the Pike estimator.[13,14] The data for most patients who had a first relapse at a locoregional site were censored for the analysis of survival

A Relapse-free Survival



No. at Risk

Dabrafenib plus trametinib	438	405	381	354	324	281	262	249	236	229	221	213	204	199	176	133	92	45	17	6	0
Placebo	432	322	263	219	199	178	168	164	157	147	143	139	136	133	121	99	69	35	13	1	0

B Relapse-free Survival, According to Subgroup

Subgroup	No. of Patients	Hazard Ratio for Relapse or Death (95% CI)
Type of *BRAF* mutation		
V600K	78	0.58 (0.32–1.06)
V600E	792	0.51 (0.42–0.62)
Sex		
Male	483	0.46 (0.35–0.58)
Female	387	0.60 (0.45–0.80)
Age		
<65 yr	712	0.54 (0.44–0.66)
≥65 yr	158	0.41 (0.26–0.62)
Disease stage (AJCC-7 criteria)		
IIIA	154	0.61 (0.36–1.06)
IIIB	356	0.50 (0.37–0.67)
IIIC	347	0.48 (0.36–0.63)
White race	859	0.52 (0.43–0.63)
Lymph-node involvement		
Micrometastasis	309	0.51 (0.36–0.72)
Macrometastasis	319	0.45 (0.33–0.61)
Micrometastasis and ulceration	143	0.51 (0.32–0.81)
Micrometastasis and no ulceration	165	0.59 (0.35–1.00)
Macrometastasis and ulceration	116	0.36 (0.21–0.57)
Macrometastasis and no ulceration	201	0.52 (0.35–0.78)
Geographic region		
United States and Canada	96	0.48 (0.25–0.92)
Europe and Israel	650	0.48 (0.39–0.59)
Australia and New Zealand	107	0.84 (0.51–1.39)
No. of nodal metastatic masses		
1	360	0.56 (0.41–0.76)
2 or 3	308	0.42 (0.30–0.57)
≥4	145	0.53 (0.35–0.80)

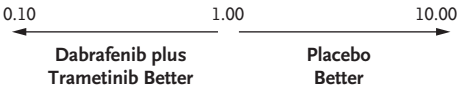


Figure 1 (facing page). Relapse-free Survival.
Shown are Kaplan–Meier estimates of relapse-free survival in the intention-to-treat population (Panel A) and a forest plot of hazard ratios for relapse or death in subgroups of patients (Panel B). The hatch marks in Panel A indicate censoring of data. AJCC-7 denotes the seventh edition of the American Joint Committee on Cancer cancer-staging manual, and NR not reached.

without distant metastasis at the time of locoregional recurrence.[12] No formal claims of statistical significance have been made, so no adjustments for multiple comparisons were performed.

RESULTS

PATIENTS

In the COMBI-AD trial, a total of 870 patients underwent randomization (438 to receive dabrafenib plus trametinib and 432 to receive placebo). The characteristics of the patients were well balanced at baseline in the two trial groups (Table S1 in the Supplementary Appendix).[10,11] All the patients had completed treatment at the time of this 5-year analysis; the last patient received the final dose of dabrafenib plus trametinib or placebo in December 2015. The full 12 months of administration of dabrafenib, trametinib, or placebo was completed by 63%, 64%, and 53% of the patients, respectively. The median daily doses of dabrafenib (284 mg) and trametinib (2 mg) were similar to the planned daily doses.[11] At the time of the data cutoff (November 8, 2019), 278 patients (63%) in the combination-therapy group and 234 (54%) in the placebo group remained in follow-up (Fig. S1 and Table S2). The minimum duration of follow-up was 59 months, and the median patient follow-up was 60 months in the combination-therapy group and 58 months in the placebo group.

RELAPSE-FREE SURVIVAL

At the data cutoff for the 5-year analysis, disease relapse or death before documented relapse had occurred in 190 of 438 patients (43%) in the combination-therapy group and in 262 of 432 (61%) in the placebo group. The median relapse-free survival was not reached (NR) in the combination-therapy group (95% CI, 47.9 to NR) and was 16.6 months (95% CI, 12.7 to 22.1) in the placebo group (hazard ratio for relapse or death, 0.51; 95% CI, 0.42 to 0.61). At 5 years, the percentage of patients who were alive without relapse was 52% (95% CI, 48 to 58) in the combination-therapy group and 36% (95% CI, 32 to 41) in the placebo group, as compared with percentages of 55% (95% CI, 50 to 60) and 38% (95% CI, 34 to 43), respectively, at 4 years (Fig. 1A). Hazard ratios for relapse-free survival favored dabrafenib plus trametinib across all patient subgroups that were evaluated (Fig. 1B). Among patients who had a relapse, a first relapse at a distant site was more common than at a locoregional site in the two groups (Table S3).

RELAPSE-FREE SURVIVAL, ACCORDING TO DISEASE STAGE

In the 5-year analysis, the duration of relapse-free survival was longer with dabrafenib plus trametinib than with placebo across all stage III substages on the basis of Kaplan–Meier analysis of survival data, according to AJCC-7 criteria. Among the patients with stage IIIA disease, the percentage of patients who were alive without relapse was 65% (95% CI, 55 to 77) with dabrafenib plus trametinib and 58% (95% CI, 46 to 72) with placebo (hazard ratio for relapse or death, 0.61; 95% CI, 0.35 to 1.07). In those with stage IIIB disease, the percentage was 55% (95% CI, 47 to 63) and 34% (95% CI, 28 to 42), respectively, with a hazard ratio of 0.50 (95% CI, 0.37 to 0.67). In patients with stage IIIC disease, the percentage was 45% (95% CI, 38 to 53) and 29% (95% CI, 23 to 37), respectively, with a hazard ratio of 0.48 (95% CI, 0.36 to 0.64) (Fig. 2). Post hoc analysis of relapse-free survival according to the revised AJCC-8 criteria showed a similar benefit with dabrafenib plus trametinib versus placebo across stage IIIA, IIIB, IIIC, and IIID disease (Fig. S2).

SURVIVAL WITHOUT DISTANT METASTASIS

At the cutoff for this analysis, a distant relapse or death before documentation of distant metastasis had occurred in 126 of 438 patients (29%) in the combination-therapy group and in 159 of 432 (37%) in the placebo group. The data for most patients who had a first relapse at a locoregional site were censored for distant relapse at the time of locoregional recurrence because follow-up for distant metastasis was not mandated by the protocol in such patients. Survival without distant metastasis favored dabrafenib plus trametinib over placebo with extended fol-

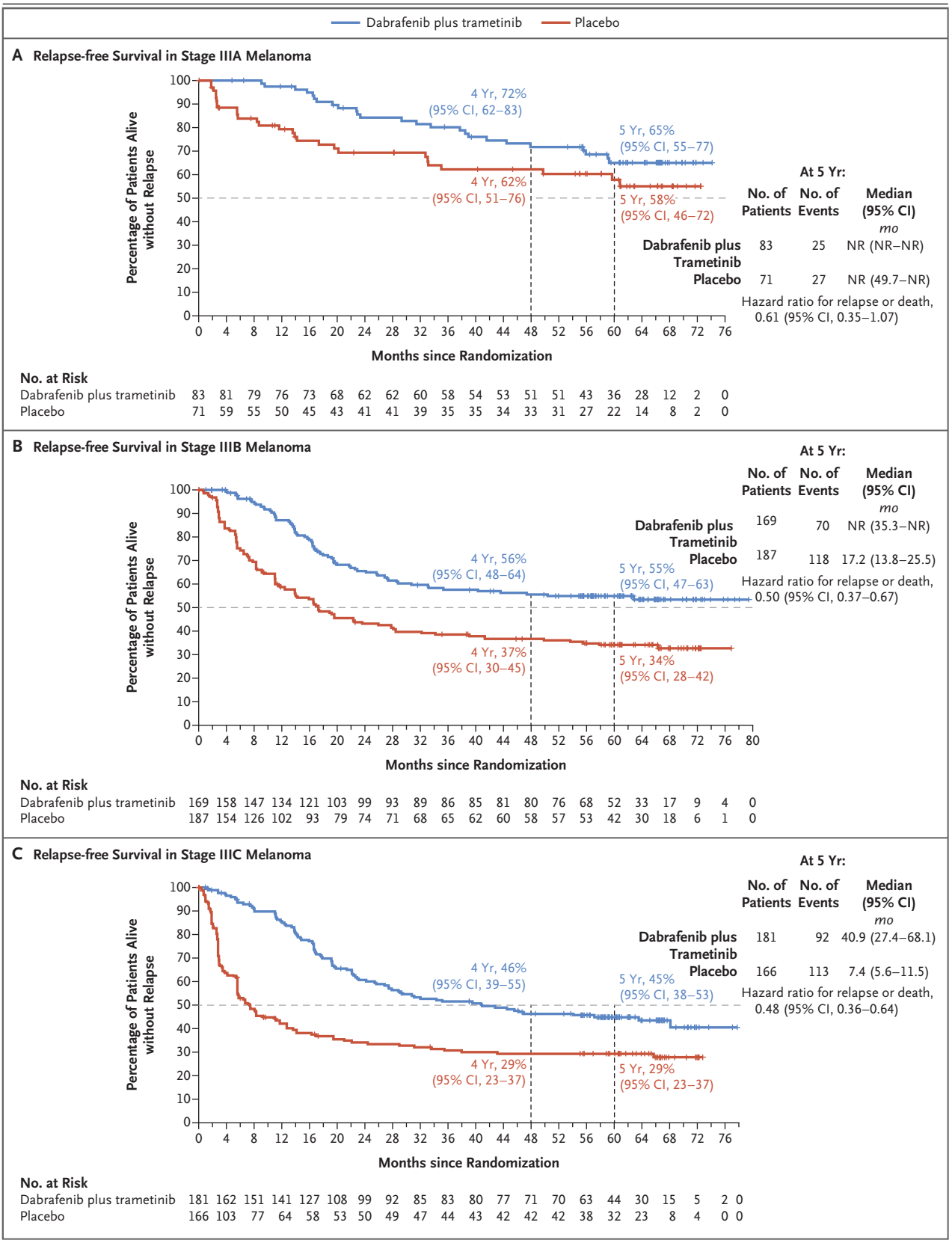

Dabrafenib plus trametinib
Placebo
A Relapse-free Survival in Stage IIIA Melanoma
Percentage of Patients Alive without Relapse
4 Yr, 72% (95% CI, 62–83)
5 Yr, 65% (95% CI, 55–77)
4 Yr, 62% (95% CI, 51–76)
5 Yr, 58% (95% CI, 46–72)
At 5 Yr:
No. of Patients
No. of Events
Median (95% CI)
mo
Dabrafenib plus Trametinib 83 25 NR (NR–NR)
Placebo 71 27 NR (49.7–NR)
Hazard ratio for relapse or death, 0.61 (95% CI, 0.35–1.07)
Months since Randomization
No. at Risk
Dabrafenib plus trametinib 83 81 79 76 73 68 62 62 60 58 54 53 51 51 43 36 28 12 2 0
Placebo 71 59 55 50 45 43 41 41 39 35 35 34 33 31 27 22 14 8 2 0
B Relapse-free Survival in Stage IIIB Melanoma
Percentage of Patients Alive without Relapse
4 Yr, 56% (95% CI, 48–64)
5 Yr, 55% (95% CI, 47–63)
4 Yr, 37% (95% CI, 30–45)
5 Yr, 34% (95% CI, 28–42)
At 5 Yr:
No. of Patients
No. of Events
Median (95% CI)
mo
Dabrafenib plus Trametinib 169 70 NR (35.3–NR)
Placebo 187 118 17.2 (13.8–25.5)
Hazard ratio for relapse or death, 0.50 (95% CI, 0.37–0.67)
Months since Randomization
No. at Risk
Dabrafenib plus trametinib 169 158 147 134 121 103 99 93 89 86 85 81 80 76 68 52 33 17 9 4 0
Placebo 187 154 126 102 93 79 74 71 68 65 62 60 58 57 53 42 30 18 6 1 0
C Relapse-free Survival in Stage IIIC Melanoma
Percentage of Patients Alive without Relapse
4 Yr, 46% (95% CI, 39–55)
5 Yr, 45% (95% CI, 38–53)
4 Yr, 29% (95% CI, 23–37)
5 Yr, 29% (95% CI, 23–37)
At 5 Yr:
No. of Patients
No. of Events
Median (95% CI)
mo
Dabrafenib plus Trametinib 181 92 40.9 (27.4–68.1)
Placebo 166 113 7.4 (5.6–11.5)
Hazard ratio for relapse or death, 0.48 (95% CI, 0.36–0.64)
Months since Randomization
No. at Risk
Dabrafenib plus trametinib 181 162 151 141 127 108 99 92 85 83 80 77 71 70 63 44 30 15 5 2 0
Placebo 166 103 77 64 58 53 50 49 47 44 43 42 42 42 38 32 23 8 4 0 0

Figure 2 (facing page). Relapse-free Survival, According to Stage III Substage.

Shown are Kaplan–Meier estimates of relapse-free survival in patients in the intention-to-treat population with melanoma of stage IIIA (Panel A), stage IIIB (Panel B), or stage IIIC (Panel C), according to the AJCC-7 criteria.

low-up. At 5 years, the percentage of patients who were alive without distant metastasis was 65% (95% CI, 61 to 71) in the combination-therapy group and 54% (95% CI, 49 to 60) in the placebo group (hazard ratio for distant metastasis or death, 0.55; 95% CI, 0.44 to 0.70) (Fig. 3). An analysis of survival without distant metastasis according to the disease stage at baseline (AJCC-7 criteria) showed similar treatment benefit favoring dabrafenib plus trametinib over placebo, regardless of the disease stage (Fig. S3).

SAFETY

The last patient received the last dose of dabrafenib plus trametinib or placebo in December 2015. There was no clinically meaningful difference between the combination-therapy group and the placebo group in the incidence or severity of serious adverse events reported during the follow-up period.

SUBSEQUENT THERAPY

A total of 173 of 435 patients (40%) in the combination-therapy group and 232 of 432 (54%) in the placebo group received subsequent therapy. The median interval between disease recurrence and subsequent therapy (excluding surgery and radiotherapy) was 7.9 weeks in the two trial groups. The most common subsequent systemic anticancer therapy was immunotherapy in the combination-therapy group (114 patients [26%]) and small-molecule targeted therapy in the placebo group (153 patients [35%]) (Table 1).

DISCUSSION

In this 5-year analysis, we found that 12 months of adjuvant treatment with dabrafenib plus trametinib conferred a durable long-term, relapse-free survival benefit for patients with resected

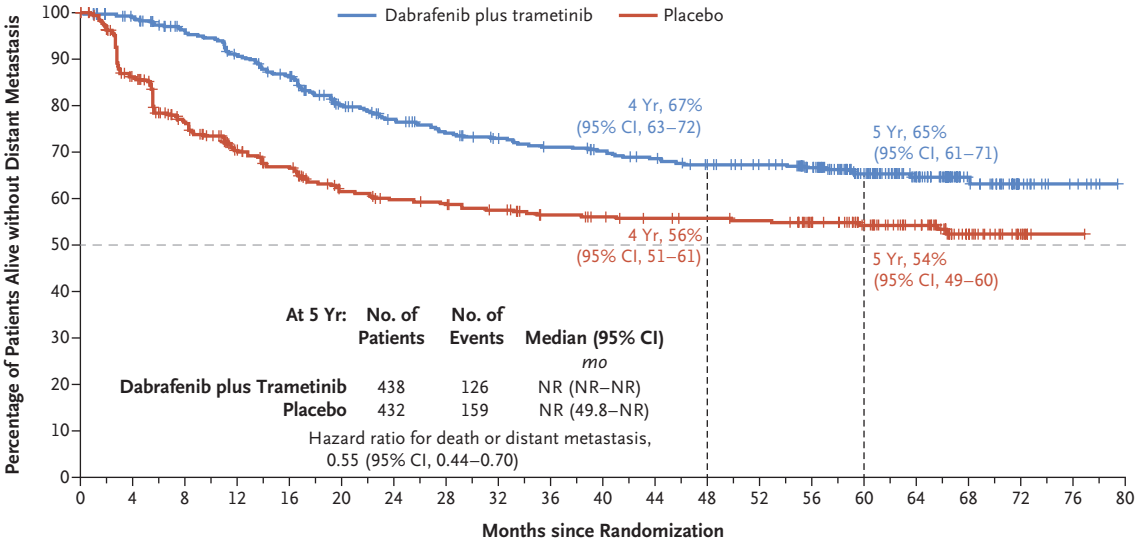


Figure 3. Survival without Distant Metastasis.

Shown are Kaplan–Meier estimates of survival without distant metastasis in the intention-to-treat population. This analysis includes patients with a distant metastasis as the site of first relapse. According to the protocol, in patients with a first relapse at a locoregional site, follow-up for distant metastases was not required, and data were censored at the time of locoregional recurrence if follow-up was not complete.

Table 1. Anticancer Therapy after Recurrence.*

Therapy	Dabrafenib plus Trametinib (N=435)	Placebo (N=432)
	no. of patients (%)	
Any anticancer therapy†	173 (40)	232 (54)
Systemic anticancer therapy		
Any therapy	148 (34)	202 (47)
Chemotherapy	23 (5)	30 (7)
Immunotherapy	114 (26)	120 (28)
Anti–PD-1	97 (22)	90 (21)
Anti–CTLA-4	71 (16)	80 (19)
Biologic therapy	8 (2)	13 (3)
Small-molecule targeted therapy	85 (20)	153 (35)

* Patients could have undergone more than one subsequent systemic anticancer therapy. CTLA-4 denotes cytotoxic T-lymphocyte–associated protein 4, and PD-1 programmed cell death 1.
† Anticancer therapies other than systemic therapy included surgery and radiotherapy.

stage III melanoma with *BRAF* V600E or V600K mutations, a benefit that persisted several years after the end of treatment. The tails of the Kaplan–Meier curves for relapse-free survival in the two groups showed evidence of stabilization, with a decrease in the number of events over time. This finding suggests that the percentage of patients who remained relapse-free long-term after surgery was higher among those who received dabrafenib plus trametinib than among those who underwent surgery alone. Longer follow-up is necessary to assess whether this lower incidence of disease recurrence will lead to a longer duration of overall survival.

The decreasing incidence of disease recurrence or death over time suggests that the Kaplan–Meier curves are reaching a plateau. In patients treated with dabrafenib plus trametinib, the estimated percentage of patients who were alive without relapse was 55% at 4 years and 52% at 5 years. Furthermore, between the time that the primary analysis was performed (median follow-up, 34 months)[11] and the time of the current analysis (median follow-up, 60 months), relapses or deaths were reported in an additional 24 patients in the combination-therapy group and in an additional 14 in the placebo group. The between-group difference in the number of events was due to the difference in the number of patients at risk during the follow-up period. Previous studies have suggested that the majority of relapses in patients with resected stage III disease occur within the initial 3 years after surgery,[15] which is consistent with the observations in the two groups in our trial. Taken together, these results suggest that treatment with dabrafenib plus trametinib does not merely delay relapse but increases the percentage of patients who are likely to remain relapse-free in the long term. Ongoing trials of anti–PD-1 therapies that enrolled patients with or without *BRAF* V600-mutated disease may show similar evidence of long-term relapse-free survival benefit. Such results are not yet available, since the latest data from the CheckMate 238 and KEYNOTE-054 trials were reported for 3-year analyses.[8,9]

Completion lymphadenectomy was part of the inclusion criteria for all three pivotal trials of current standard-of-care adjuvant therapies.[6,7,11] However, based on the results of the Multicenter Selective Lymphadenectomy Trial II (MSLT-II) and the German Dermatologic Cooperative Oncology Group (DeCOG) trial, relevant guidelines have been amended and no longer require completion lymphadenectomy in most patients with stage III disease.[4,5,16,17] We are not aware of any data suggesting differential benefit for any standard-of-care adjuvant systemic therapy in patients with or without completion lymphadenectomy.

Durable survival without distant metastasis favoring the combination-therapy group was also observed with extended follow-up, with the two groups showing a plateau at the tail of the Kaplan–Meier curves. Since the time of the primary analysis,[11] distant relapse or death before documentation of distant metastasis was reported in 16 patients who received dabrafenib plus trametinib and in 7 who received placebo. The analysis involving patients who survived without distant metastasis included those who had a distant metastasis as their first site of relapse; most patients with a first locoregional relapse were not followed for the occurrence of distant metastasis. Although the informative censoring in this trial deviates somewhat from the intention-to-treat principle, it is likely to favor the placebo group, which had a higher number of patients with a first relapse at a locoregional site than did the combination-therapy group.[12] Therefore,

the benefit in the combination-therapy group for survival without distant metastasis may be underestimated.

At the time of the earlier reported interim analysis that was based on an information fraction of 26%, overall survival results favored combination therapy with dabrafenib plus trametinib over placebo, but the prespecified interim significance threshold of P=0.000019 was not met.[11] At the current data cutoff, a total of 216 deaths were reported in the two trial groups, and the per-protocol number of events (approximately 299) to trigger the final overall survival analysis had not been reached. In the absence of long-term overall survival data, the Weibull mixture model for cure rate estimation provides a method to assess long-term outcomes through estimation of the percentage of patients who may not have a relapse. Notably, overall survival in our trial may be affected by the 47% of patients who received subsequent anticancer therapy; a strength of cure rate modeling is that it is based on relapse-free survival and thus not influenced by subsequent therapies. However, it does rely on the assumption that a subgroup of patients will be cured, which cannot be empirically tested. Estimated cure fractions that are based on the previous data cutoff (on April 30, 2018) were 54% (95% CI, 49 to 59) in the combination-therapy group and 37% (95% CI, 32 to 42) in the placebo group.[10] The current analyses provide further support for these long-term survival benefits as we await the final overall survival analysis.

Updated safety analyses were not performed at this data cutoff because no patients were continuing to receive therapy during the extended follow-up period, and reporting of treatment-related adverse events after that point was at the investigator's discretion. The vast majority of patients had treatment-related adverse events only during the initial 12-month treatment window. Nearly all the adverse events that were associated with dabrafenib plus trametinib were transient and resolved after the discontinuation or interruption of treatment, as expected on the basis of the mechanisms of action and pharmacokinetic measurements of these agents.[18,19] Both the benefits and risks of treatment should be taken into consideration and discussed with patients for informed decision making regarding therapy.

Overall, this 5-year analysis featuring extended follow-up from the phase 3 COMBI-AD trial confirms that 12 months of adjuvant therapy with dabrafenib plus trametinib led to durable long-term benefit regarding relapse-free survival in patients with resected stage III melanoma with *BRAF* V600 mutations. The effect of adjuvant therapy with dabrafenib plus trametinib on long-term overall survival remains to be determined.

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APPENDIX

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